

None of these amendments adds new matter, and applicants respectfully request that the amendments be entered.

REMARKS

Applicants respectfully request reconsideration of this application in view of the foregoing amendments and the following remarks.

Rejection Under 35 U.S.C. § 112, first paragraph

Pending claims 1-11 and 22-29 stand rejected under 35 U.S.C. § 112, first paragraph as “containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.” “The sole fragment which remains non-enabled is single chain immunoglobulins.”

Applicants have amended the claims that recite single chain immunoglobulins to delete all reference to “single chain immunoglobulins,” as suggested by the Examiner. Despite this amendment, applicants believe that the use of single chain immunoglobulins according to applicants’ invention is fully enabled by the application as filed and the state of the art as of the filing date. The field of single chain antibodies was sufficiently developed such that one of skill in the art could, without undue experimentation, create a library of single chain antibodies for use in the methods described by applicants. Applicants reserve the right to prosecute claims directed to methods of using single chain immunoglobulins in the

inhibition of lymphoma metastasis and treatment of lymphoma in subsequent continuation applications. In view of the amendments, applicants respectfully request that the Examiner withdraw the rejection of claims 1-11 and 22-29 under 35 U.S.C. § 112.

Rejections Under § 102(b)

Each of the pending claims stands rejected under 35 U.S.C. § 102(b) in view of several references that show the use of IVIG in treating secondary infections in patients who also have lymphoma. None of the cited references, however, indicate that the lymphoma is metastatic. Applicants have amended the rejected claims such that each requires the use of IVIG or fragments thereof in the inhibition of lymphoma **metastasis** or treatment of **metastatic** lymphoma. Such methods are not inherently performed by the prior art.

Applicants' specification defines "metastasis" as "the transfer of malignant tumor cells, or neoplasm, via the circulatory or lymphatic systems or via natural body cavities, usually from the primary focus of neoplasia to a distant site in the body, and subsequent development of secondary tumors or colonies in the new location." (specification at page 4, lines 22-27). Inhibition of this process is not shown by any of the cited references. The instant specification further defines "inhibition of metastasis" as "preventing or reducing the development of metastases," where "metastases" are "secondary tumors or colonies formed as a result of metastasis." (specification at page 4, lines 28-31). The cited references also do not show inhibition of metastasis as defined by the specification, nor do they show treatment of metastatic lymphoma.

Each of the claims rejected under § 102(b) require metastatic lymphoma to be present in order for IVIG administration to effect inhibition or treatment. This is clear from the claim language itself, as well as from the specification, which shows that in each of the experimental examples involving administration of IVIG to mammals, inhibition of metastatic cancer is inhibited (see examples 1-5 and 7).

Given the definitions in the specification and the requirement for “inhibition of metastasis” or “treatment of metastatic lymphoma” in each of the rejected claims, it is clear that none of the prior art references cited by the Examiner anticipates the instant invention. Chapel et al.

The Examiner has rejected claims 1-2, 7-9 and 25-28 under 35 U.S.C. § 102(b) based on Chapel et al.* The Examiner contends that because Chapel et al. did not report metastatic lymphoma, this reference points to the efficacy of the treatment. This logic is flawed -- in the absence of any indication that the lymphoma in question was of a metastatic nature, the failure of Chapel et al. to note metastasis is a negative result -- nothing about metastasis in this study can be inferred one way or the other. The non-Hodgkin's lymphoma described in Chapel et al. could have been metastatic or non-metastatic -- each scenario is possible and plausible. If there was no metastasis present, then no inhibition of metastasis can have occurred, and no inherent anticipation can have occurred, because each of the rejected claims requires the inhibition of metastasis or treatment of metastatic

* Chapel et al., “A Crossover Study Of The Use Of Intravenous Immunoglobulin For Prophylaxis Against Infection In Patients With Chronic Lymphocytic Leukemia Or Low Grade Non-Hodgkins Lymphoma,” Clin. Res. 36, pp. 407A (1988).

lymphoma. One cannot assume that metastasis was an element of the study based on probability or possibility.

Rapoport v. Dement, a case recently decided by the Federal Circuit, confirms that inherency may not be established by probabilities or possibilities. In Rapoport, the Court held that a count claiming a “method of treating sleep apneas” was not anticipated by a prior art reference treating symptoms of sleep apneas, where no evidence was presented that the prior art reference actually treated the underlying respiratory disorder. The Court warned against making certain “speculative assumptions” in determining inherency, reiterating that “[i]nherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing **may** result from a given set of circumstances is not sufficient” Rapoport v. Dement, 59 USPQ2d 1215, 1222 (Fed. Cir. 2001) (emphasis in original) (citations omitted).

Similarly, here, each of the prior art references cited by the Examiner for anticipation only show IVIG treatment of secondary infections or symptoms **other** than metastasis of lymphoma. There is no disclosure in the cited references of the use of IVIG in patients with metastatic lymphoma with the intent to inhibit metastasis of the lymphoma or treat the lymphoma itself. Indeed, there is no evidence that IVIG was used in the treatment of metastatic lymphoma in the cited references. In each case, it is possible that IVIG treatment was carried out in patients having a primary tumor only.

To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either expressly or inherently. Rapoport at 1218 (citation omitted).

Here, the cited references do not disclose every limitation of the claimed invention. The cited references do not inherently disclose inhibition of metastasis of lymphoma or treatment of metastatic lymphoma, because the assumption cannot be made that the lymphoma described in the cited references was in fact metastatic.

As stated by the Federal Circuit in In re Derwood L. Runion, “if the crucial property or characteristic of the reference is not necessarily implicit in the reference’s disclosure, then the principles of inherency do not apply and a reference without either inherent or explicit disclosure of each and every element of the claim cannot anticipate the claim.” In re Derwood L. Runion, 1993 U.S. App. LEXIS 1945 (Fed. Cir. 1993).^{*} Here, “metastatic lymphoma” is not necessarily implicit in the cited references’ disclosure of various lymphomas. Therefore the cited references do not inherently disclose inhibition of metastasis of lymphoma or treatment of metastatic lymphoma by IVIG.

The existence of metastatic lymphoma does not flow naturally from the cited references. A determination of the metastatic nature of a given lymphoma would have to be conducted clinically for this to be known. It is equally possible that none of the described lymphomas were metastatic, that some of the described lymphomas were metastatic or that all of the described lymphomas were metastatic. One cannot tell from the disclosures in question which of these possibilities is the case. For this reason, it cannot be established that

^{*} Though an unpublished and therefore non-precedential case, applicants believe that the cited language is representative of the Federal Circuit’s view of the inherency doctrine. The quoted passage was the Court’s conclusion regarding inherency based on a citation from Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264 (Fed. Cir. 1991).

metastatic lymphoma was present in the cited references as a matter of scientific fact such that the cited references inherently disclose the inhibition of lymphoma metastasis with IVIG.

Applicants therefore take exception to Examiner's statement that "the function of inhibiting metastasis is a result of the administration of IVIG, in view that Chapel *et al* administered IVIG to a mammal with lymphoma . . ." In Chapel et al., there is no evidence that metastatic lymphoma was present at the time of IVIG administration. Without certain proof that the lymphoma in Chapel et al. was metastatic, Chapel et al. cannot be deemed to anticipate applicant's invention.

Thus, applicants respectfully request that the Examiner withdraw the rejection of claims 1-2, 7-9 and 25-28 under 35 U.S.C. § 102(b).

Morell et al.

The Examiner has rejected claims 1-3, 7-10, 25 and 28 under 35 U.S.C. § 102(b) based on Morell et al.* Applicants traverse.

Like Chapel et al., Morell et al. does not provide any evidence that metastatic lymphoma was present at the time of IVIG administration. For all of the reasons set forth above regarding the deficiency of the evidence supporting a case of inherent anticipation by Chapel et al., Morell et al. does not anticipate the pending claims.

Thus, applicants respectfully request that the Examiner withdraw the rejection of claims 1-3, 7-10, 25 and 28 under 35 U.S.C. § 102(b).

* A. Morell and S. Barandun, "Prophylactic and Therapeutic Use of Immunoglobulin for Intravenous Administration in Patients with Secondary Immunodeficiencies Associated with Malignancies," Pediat. Infect. Dis. J. 7, pp. S87-S91 (1988).

Besa et al.

The Examiner has rejected claims 1-2, 7-9 and 25-28 under 35 U.S.C.

§ 102(b) based on Besa et al.* Applicants traverse.

Like Chapel et al. and Morell et al., Besa et al. does not provide any evidence that metastatic lymphoma was present at the time of IVIG administration. For all of the reasons set forth above regarding the deficiency of the evidence supporting a case of inherent anticipation by Chapel et al., Besa et al. does not anticipate the pending claims.

Thus, applicants respectfully request that the Examiner withdraw the rejection of claims 1-2, 7-9 and 25-28 under 35 U.S.C. § 102(b).

Rejections Under § 103

The Examiner has rejected claims 1-3, 5-11, 22 and 25-28 under 35 U.S.C.

§ 103(a) based on several documents. In particular, the Examiner maintains that the rejected claims are unpatentable over Morell et al. or Besa et al. in view of Cafiero et al., Webb et al. and Way. Applicants traverse.

The cited references all differ from the claimed invention in that none of the cited references teach or suggest that administration of IVIG is useful for inhibiting metastasis of lymphoma or for the treatment of lymphoma. Nor do any of the cited references suggest a combination with other references to supply the missing information.

* Besa et al., Am. J. Med. 84, pp. 691-698 (1988).

A skilled artisan, searching for methods of inhibiting metastasis or for treating lymphoma, armed with the above documents, would have absolutely no motivation whatsoever to look at any of the documents at all, let alone combine the documents in the manner suggested by the Examiner, to arrive at the invention of claims 1-3, 5-11, 22 and 25-28. The Examiner's combination of these references is improper and ineffective, since none of the references even mention the inhibition of metastasis of lymphoma or treatment of metastatic lymphoma, to which applicant's claims are directed.

A retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements in the particular claimed combination. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown. In re Newell, 891 F.2d 899, 901, 13 USPQ2d 1248, 1250 (Fed.Cir. 1989).

Webb et al. discusses therapies for lymphoma treatment **other than IVIG**. Morell et al., Besa et al., Cafiero et al. and Way each discuss the use of IVIG for purposes **other than inhibiting metastasis of lymphoma or treating metastatic lymphoma**. None of these references teach or suggest that the IVIG used to prevent secondary infections had any role in the inhibition of metastasis of lymphoma or in the treatment of metastatic lymphoma. An inherent use of IVIG in patients with lymphoma cannot render applicants' invention obvious. The effect of the use of IVIG in the inhibition of lymphoma metastasis or in the treatment of metastatic lymphoma was not clinically measured in any of these

references, and therefore no effect of IVIG, beneficial or otherwise, directly on the lymphoma can have been observed by one of skill in the art.

Examiner has cited In re Dillon, 16 USPQ2d 1897 (Fed. Cir. 1990) for the proposition that “applicant’s newly discovered properties must be considered in determining whether a prima facie case of unpatentability is made, along with all the other evidence. Neither structure nor properties can be ignored; they are essential to consideration of the invention as a whole. But discovery of a property of a compound is not evidence in determining whether the prior art makes a case of prima facie obviousness.”

Applicants respectfully assert that In re Dillon is inapposite. The Court in Dillon followed cases holding that “if an examiner considers that he has found prior art close enough to the claimed invention to give one skilled in the relevant chemical art the motivation to make close relatives (homologs, isomers, etc.) of the prior art compound(s), then there arises what has been called a presumption of obviousness or a *prima facie* case of obviousness.” Dillon at 1904. Here, however, the field is not the chemical arts, and we do not have a situation where close relatives of a chemical compound are asserted for obviousness. Dillon is therefore inapposite.

Moreover, the Court in Dillon held that **composition claims**, which are not limited to any new use, may be found obvious over prior art compositions of similar structure and properties. The Court explicitly stated in Dillon that it reviewed only the merits of the composition claims. Here, however, **applicants’ method claims are limited to the new**

uses of inhibiting metastasis of lymphoma or treating metastatic lymphoma, which are not properties suggested by any of the cited prior art references.

Here, a finding of obviousness fails for at least two reasons. First, the prior art methods of treating secondary infections do not exhibit similar properties to the claimed methods of inhibiting metastasis of lymphoma. In contrast, the prior art reference compound in Dillon (tri-orthoester fuel compositions) and the claim compound (tetra-orthoester fuel compositions) were both known to have similar properties, supporting the holding of *prima facie* obviousness of the claimed compounds. This, together with structural similarity, was the basis for the obviousness finding in Dillon.

Second, applicants' method claims are limited to a specific use not taught by the prior art. As such, any cited prior art references must suggest the specific use claimed by applicants to support a finding of obviousness. Three criteria must be met by the Examiner in order to establish a *prima facie* case of obviousness: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not be based on applicant's disclosure. MPEP 2142.

The MPEP further states that when the motivation to combine the teachings of the references is not immediately apparent, it is the duty of the Examiner to explain why the combination of the teachings is proper. MPEP 2142.

The Examiner states that “the motivation for administering IVIG . . . to a mammal subcutaneously has been established relying solely on the teachings of the demonstrated success of IVIG administration to a mammal via intravenous administration, as well as the knowledge by those of skill in the art that IVIG was routinely administered subcutaneously as set forth by Webb *et al.*” This “success” cited by the Examiner, however, is success only in treating secondary infections, **not inhibiting metastasis or treating metastatic lymphoma.**

Each element of a *prima facie* case for obviousness remains unproven. First, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. For example, Morell et al., Besa et al., and Cafiero et al. do not teach the inhibition of metastasis or treatment of metastatic lymphoma with IVIG, a necessary element of the claimed invention. At most these references teach that IVIG can be used to treat secondary infections in cancer patients. Any “inherent” disclosure in these references cannot be used in an obviousness analysis. Nor do Webb et al. or Way provide the missing suggestion to use IVIG in the inhibition of metastasis. It is improper hindsight, in view of applicants’ specification, to find applicants’ invention obvious in view of these references. There is no teaching in any of them, alone or combined, that IVIG is efficacious in the

inhibition of metastasis or treatment of lymphoma, necessary elements of the claimed invention.

Furthermore, given the cited references, there can be no reasonable expectation that IVIG would be successful in inhibiting metastasis, because none of the cited references, alone or together, either explicitly or implicitly, suggest such a result. Indeed, no effect of IVIG on metastasis of lymphoma is ever measured in any of these references.

Finally, none of the cited prior art references, alone or combined, teach or suggest all the claim limitations of the rejected claims. Each reference fails to teach the inhibition of metastasis limitation of claims 1-11, and each reference also fails to teach the treatment of metastatic lymphoma limitation of claims 22-29. As described above in the discussion of inherent anticipation, it cannot be shown that the cited references necessarily even treated metastatic lymphoma, let alone inhibited it with IVIG. All three requirements of a *prima facie* case of obviousness are thus absent.

Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 1-3, 5-11, 22 and 25-28 under 35 U.S.C. § 103(a).

Double Patenting

Claims 1-11 and 22-29 stand rejected as unpatentable over issued claims 1-18 of U.S. patent 5,965,130 and issued claims 1-10 of U.S. patent 5,562,902 under the obviousness-type double patenting doctrine. Applicants remain ready to submit a terminal

disclaimer in compliance with 37 C.F.R. § 1.321(c) upon an indication by the Examiner that all other rejections are withdrawn.

New Rejection Under § 102(b)

Examiner has rejected claim 29 under 35 U.S.C. § 102 in view of Vitetta et al. The Examiner asserts that Vitetta et al.* disclose intravenous administration of Fab' fragments to a mammal with B-cell lymphoma, thereby anticipating the claimed invention. Applicants traverse.

Vitetta et al. disclose the use of the Fab' fragment of a monoclonal anti-CD22 antibody (RFB4) coupled to chemically deglycosylated ricin A chain. This is not IVIG as defined in applicants' specification. Applicants have defined "IVIG" as "gamma globulin preparations suitable for intravenous use, such as those IVIG preparations commercially available from several sources," and "gamma globulin" is defined as "the serum globulin fraction that is mainly composed of IgG molecules." (specification at page 4, lines 13-18). One of skill in the art would understand from these definitions and from the examples of the specification that IVIG is a term of art that refers to preparations of the serum globulin fraction of broad specificity suitable for intravenous use (see also specification at page 5, lines 5-19). IVIG would be understood **not** to comprise preparations of individual monoclonal antibodies as used in Vitetta et al.

* Vitetta et al., Cancer Research, Vol. 51, pp. 4052-4058 (1991).

Vitetta et al. does not anticipate the instant invention because IVIG is not used in the study. Vitetta et al. also does not inherently anticipate the claimed invention, for the reasons enumerated above in applicants' discussion of Chapel et al., Morell et al. and Besa et al. Specifically, Vitetta et al. does not definitively disclose inhibition of metastasis of lymphoma or treatment of metastatic lymphoma. Applicants therefore respectfully request that the Examiner withdraw the rejection of claim 29 under 35 U.S.C. § 102.

Withdrawal of Final Rejection

The Examiner's rejection of claim 29 under 35 U.S.C. § 102 in view of Vitetta et al. is a new ground of rejection. Vitetta et al. is a new reference not cited prior to the Examiner's June 6, 2001 office action. MPEP§ 706.07(a) states that "[a] second or any subsequent action on the merits in any application or patent involved in reexamination proceedings should not be made final if it includes a rejection, on limitations which should reasonably have been expected to be claimed. It is applicants' view that it was reasonable to expect that the subject matter of added claim 29 would be claimed based on the disclosure and the other claims in the application as filed (see, e.g., specification at page 7, lines 8-10 and claim 12 as originally filed).

Applicants therefore respectfully request that the Examiner withdraw the finality of the June 6, 2001 office action, thereby affording applicants a further opportunity to respond to this new ground of rejection, if the Examiner does not withdraw it in response to this Amendment and Reply.

For all of the above reasons, applicants submit that each of the pending claims are now in condition for allowance and request that this application be passed to issue. However, if the Examiner believes that an interview would facilitate the resolution of any outstanding issue, the Examiner is kindly requested to contact the undersigned.

Respectfully submitted,



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